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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/750,280 | 12/29/2000 | D. Scott Wilbur | 33700WC005 | 6495 |

441 7590 11/17/2004

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| EXAMINER | |
|---|---|
| KANTAMNENI, SHOBHA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/750,280 | WILBUR ET AL. | |
| | Examiner | Art Unit | |
| | Shobha Kantamneni | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *33,34,36,38 and 40-97* is/are pending in the application.

4a) Of the above claim(s) *42-54,60,61,63,68,69,71,72,75-87 and 90-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33, 34, 36, 38, 40, 41, 55-59, 62, 64-67, 70, 73-74, 88-89, 98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/01/2004 has been entered.

Claims 33, 34, 36, 38, and 40-98 are pending. Claims 42-54, 60, 61, 63, 68, 69, 71, 72, 75-87 and 90-97 are withdrawn from consideration. The Amendments filed on 07/01/2004 amended claims 33, 70, 73 and 74.

Applicant's amendments to claim 33 by introducing "aspartyl moiety" overcomes the Double patenting rejection of claims 33-41, 55-59, 62, 64-67 and 70 under U.S.C. 101 over the copending Application 09/519998.

Applicant's amendment to claim 33 is sufficient to overcome rejection of claims 33-35, 39-41, 55-59, 62, 64-67, 73-73 and 88-89 under 35 U.S.C 102(b) as being unpatentable over Wilber, and the rejection of claims 33-41, 55-59, 62, 64-67, 70, 73-74 and 88-89 under 103(a).

Applicant's amendment to claims 33-41, 54-59, 62, 64-67 and 70-74 is sufficient to overcome the rejection under 35 U.S.C. 112 second paragraph.

The Amendments to the claims necessitated the following new rejections.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 73-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnosis of myocardial infraction and certain cancers and treatment of certain cancers, does not reasonably provide enablement for **diagnosis and treatment of any condition or disease in a mammal**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

**(1) The nature of the invention:**

The invention provides a molecule of structure (I) with at least three functional parts comprising a trifunctional cross-linking moiety that is linked via a linker to an affinity ligand, a biomolecule reactive moiety, and an effector agent.

**(2) The state of the prior art:**

The prior art teaches trifunctional compounds as recited in instant claim 1. However, the art does not teach all the possible compounds encompassed by structure (I) of instant claim 1. See WO 97/29114. Additionally, WO 97/29114 teach that one compounds of structure (I) can be used for the diagnosis of certain cancers and myocardial infarcts and the treatment of certain cancers.

**(3) The relative skill of those in the art:**

The relative skill of those in the art is high.

**(4) The predictability or unpredictability of the art:**

The unpredictability of the art is very high because there are thousands of diseases which have fundamentally different mechanism and different causes. The method of diagnosing or treating one disease or condition does not necessitate the treatment or diagnosis of another disease or condition since diseases and conditions have unique chemical pathways by which they are expressed. Additionally, a single disease or condition can be diagnosed via multiple biochemical pathways and treated via multiple biochemical pathways. Thus, the treatment and diagnosis of diseases and conditions is highly unpredictable. The scope of enablement varies inversely with the

degree of unpredictability of the factors involved, and physiological activity is generally considered to be unpredictable factor.

**(5) The breadth of the claims:**

The claims are very broad. The claims are drawn to a reagent of structure (I) for the **diagnosis and treatment of unknown list of conditions or diseases** in a mammal. The coverage of diseases in the claim is immense. The breadth of the claims includes hundreds of diseases such as cancer, pulmonary disorders, etc. Even within cancer, there are hundreds of types of cancers and tumors. Thus there is no such thing as the **treatment or diagnosis** of these unknown list of conditions as claimed using one reagent of structure (I).

**(6) The amount of direction or guidance presented:**

Pages 2-3 of the specification provide support for the diagnosis of myocardial infarcts and for the diagnosis and treatment of the cancers recited on pages 2-3. However, this is the only guidance the specification presents regarding the diseases and conditions that can be diagnosed or treated using the instant compound of structure (I). The remainder of the specification is directed toward the specifics of the compounds of structure (I) and a method of making them.

**(7) The presence or absence of working examples:**

Pages 21-23 provide examples, but these examples are all directed toward methods of making the compounds of structure (I). There are no working examples for the diagnosis or treatment of the various diseases using compounds of structure (I).

**(8) The quantity of experimentation necessary:**

Since every disease and disorder has its unique chemical pathway of expression, diagnosis and treatment of individual diseases and condition cannot be predicted a priori but must be determined from case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine which compounds of structure (I) treats which diseases/conditions and diagnosis which diseases/conditions. For example, chemical modification of biomolecules may alter the biological property that is important in the use of that particular molecule e.g. targeting cancer cells and also other properties such as solubilities in aqueous media, binding affinities etc. Thus variety of compounds encompassed by structure (I) will have different biological properties. Considering vast variety of compounds covered by structure (I) and the multitude of different diseases to be diagnosized and treated, this is a very large degree of experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 70 and 98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no antecedent basis for the coupling agents N-methyl glycyl residue in linker 1, structures 39, 43; an N-methyl group in linker 1, structure 40; structures 41, 42. The Applicant amends claim 70 to include “wherein compounds 41 and 42 are stabilized against enzymatic cleavage by biotinidase”, but the structures 41 and 42 do not represent this change.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33, 34, 40, 41, 55-59, 62, 64-67, 70, 73-74, 88-89, 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilber et al. (WO 97/29114) and further in view of Rosebrough, The Journal of Pharmacology and Experimental Therapeutics, vol 265, No.1, 1993, 408-415.

The instant invention is directed toward a single molecule reagent comprising a trifunctional cross-linking moiety, an affinity ligand, a biomolecule reactive moiety, an effector agent, and optionally three linkers.

Wilbur et al. disclose water soluble biotin-containing compounds and biotinylation reagents incorporating soluble linker moieties. They teach that biotin-containing compounds and biotinylation reagents may also comprise moieties that provide additional properties such as biotinidase-stabilizing properties. Suitable water soluble linkers comprise at least two coupling or reactive groups allowing the linker to bind to both a biotin moiety and another functional moiety. Functional moiety can be trifunctional. The water soluble linker moieties are diamino-ether moiety such 4, 7,10-trioxa-1,13-tridecanediamine or 2,2'-(ethylenedioxy)diethylamine or tetraethylene glycol,

diamino-thioether molecules. The water soluble linker may be coupled to a biotin moiety through an amide forming reaction employing a amine group on the linker and the carboxylate site on a biotin moiety. The amide forming reaction may include the use of coupling agents. Wilbur further teaches that the linker moiety attached to the biotin moiety is modified under certain conditions by introduction of a steric group such as carboxylates, larger alkyl groups, aryl groups etc. alpha to the amine (or another functionality) of the linker, to provide resistance to cleavage by biotindase. Modifications of biotin by conjugation with water soluble linkers possessing a branched chain alpha methyl group such as a 3-aminobutyric acid, 1,2-diaminopropane, are desirable to produce conjugates more resistant to *in vivo* degradation by the enzyme biotinidase. Wilbur teaches that by combining a variety of biotin moieties with the carboxylate coupled steric moieties and a water soluble linker moiety, water soluble biotin compounds having varying binding affinities with biotin-binding proteins and enhanced resistance to *in vivo* degradation are obtained. Exemplified is a trifunctional reagent comprising tricarboxybenzene as the trifunctional cross-linking agent, biotin as the affinity ligand, maleimide as the biomolecule reactive moiety, iodinated benzene as the effector agent, and trioxadiamine as linker 1, linker 2, and linker 3. See page 17, lines 26-30; page18, lines1-12; and pages 38-39.

Wilbur et al. does not teach "aspartly moiety " in linker 1 of the affinity ligand as a stabilizing moiety to inhibit enzymatic cleavage.

Rosebrough teaches the pharmacokinetics, and *in vivo* and *in vitro* stability of radiolabeled deferoxamine-biotin derivatives in plasma. See abstract. Rosebrough

teaches that introduction of a carboxyl group alpha to the amide bond of biotinamide, blocks the biotinidase activity, thereby increasing the stability of biotinamide bond towards enzymatic cleavage and also the binding ability towards avidin *in vivo* and *in vitro* is still maintained. See page 410; page 414, lines 35-40.

From the teachings of Wilber and Rosebrough, it would have been obvious to one having ordinary skill in the art at the time the invention was made, to use aspartyl moiety in linker 1 of the affinity ligand because (1) Rosebrough teaches that by introducing an alpha carboxylate group to the amide bond in the linker 1 increases stability towards enzymatic cleavage, thus by introducing an aspartyl moiety in linker 1 introduces a beta carboxylate group to the amide bond in the linker 1, which is a homologue of alpha carboxylate, 2) a homologous series is a family of chemically related compounds, the composition of which varies from member to member by $CH_2$ * * *, wherein Chemists knowing the properties of one member would in general know what to expect in adjacent members (In re Henze, 85 USPQ 261, 261 (CCPA 1950)); thus, one of skill in the art would have been motivated to teach "Aspartyl moiety" as alpha-carboxylate in linker 1 a) because of the expectation of achieving the same binding with avidin or streptavidin and b) because adjacent homologs are considered to be obvious variants absent unexpected results.

It is respectfully pointed out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Thus, in the instant case, the intended use of the reagent is not afforded patentable weight.

Claims 36, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilbur et al. and Rosebrough as applied to claims 33, 34, 40, 41, 55-59, 62, 64-67, 70, 73-74, 88-89, 98 above, and further in view of Griffiths (5,482,698).

Wilbur et al. is applied as discussed above. The reference lacks homobiotin as the affinity ligand, wherein homobiotin contains 1 additional "CH2" member in the biotin alkyl chain.

Griffiths teaches detection and therapy of lesions with biotin/avidin polymer conjugates. The reference teaches that commercial biotin products are available in which the biotin has been modified by the addition of alkyl groups to alter the binding capacity of biotin. See Col. 8, lines 39-45.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to teach the biotin of Wilbur et al. as homobiotin because a) Wilbur et al. teach that many modified forms of biotin have been synthesized for various applications, such as providing reversible binding to a biomolecule, and are useful in their invention, and Griffiths teaches that the addition of a -CH2- group to biotin is a known commercial product that is relied upon to change the binding properties of biotin; b) a homologous series is a family of chemically related compounds, the composition of which varies from member to member by CH2 * * *, wherein Chemists knowing the properties of one member would in general know what to expect in adjacent members

(In re Henze, 85 USPQ 261, 261 (CCPA 1950)); thus, one of skill in the art would have been motivated to teach biotin as homobiotin a) because of the expectation of achieving reversible binding and b) because adjacent homologs are considered to be obvious variants absent unexpected results.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 33, 34, 36, 38, 55-59, 62, 64-67, 70, 73-74, 88-89, and 98 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, 17-19, and 21-23 of copending Application No. 09/519998. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no patentable distinction between the two sets of claims.

The proviso at the end of claim 1 of 09/519,998 avoids overlap. However, the claimed stabilizing moieties towards enzymatic cleavage of the biotinamide bond such as alpha carboxylate of '998' and the use of aspartyl moiety which results in beta

carboxylate are homologues. It would have been obvious to one having ordinary skill in the art at the time the invention was made, to use aspartyl moiety in linker 1 of the affinity ligand because a homologous series is a family of chemically related compounds, the composition of which varies from member to member by $CH_2$ * * *, wherein Chemists knowing the properties of one member would in general know what to expect in adjacent members (In re Henze, 85 USPQ 261, 261 (CCPA 1950)); thus, one of skill in the art would have been motivated to teach "Aspartyl moiety" as alpha-carboxylate in linker 1 a) because of the expectation of achieving the same binding with avidin or streptavidin and b) because adjacent homologs are considered to be obvious variants absent unexpected results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response to Applicant's Arguments/Amendment***

Applicant argue's that Wilber does not qualify as prior art under 35 U.S.C 102(b). This argument is not persuasive. It is respectfully pointed out that the claimed priority to PCT/SE98/01345 is not submitted timely. Also, there is an ambiguity concerning whether the asserted claim for PRIORITY to PCT/SE98/01345 which was filed on July 7, 1998 is under 35 U.S.C 120 or 35 U.S.C 119 (a-d). In either case the claim for priority to this document is ultimately 07/07/1999.

The foreign priority claim filed on 02/28/2002 was not entered because the foreign priority claim was not filed during the time period set forth in 37 CFR 1.55(a)(1). For original applications filed under 35 U.S.C. 111(a) (other than a design application)

on or after November 29, 2000, the time period is during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior foreign application. For applications that have entered national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the claim for priority must be made during the pendency of the application and within the time limit set forth in the PCT and the Regulations under the PCT. See 37 CFR 1.55(a)(1)(ii). If applicant desires priority under 35 U.S.C. 119(a)-(d), (f) or 365(a) based upon a prior foreign application, applicant must file a petition for an unintentionally delayed priority claim (37 CFR 1.55(c)). The petition must be accompanied by (1) the claim (i.e., the claim required by 35 U.S.C. 119(a)-(d) and (f) and 37 CFR 1.55) for priority to the prior foreign application, unless previously submitted; (2) a surcharge under 37 CFR 1.17(t); and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.55(a)(1) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

For examining purposes the effective US priority date is 07/07/1999.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER